IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 3648
de la MONTE *et al.*	Art Unit: 1635
Appl. No. 09/964,667	Examiner: McGarry, S.
Filing Date: September 28, 2001	Atty. Docket: 0609.4370005/RWE/FRC
For: **Transgenic Animals and Cell Lines for Screening Drugs Effective for the Treatment or Prevention of Alzheimer's Disease**	

Reply Brief Under 37 C.F.R. § 41.41

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Commissioner for Patents
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Sir:

Appellants filed a Brief on Appeal to the Board of Patent Appeals and Interferences for the above-captioned application on April 8, 2005. The appeal is directed to the final rejections of claims 35-45 under 35 U.S.C. § 112, first paragraph, as set forth in the Office Action dated September 9, 2004. The Examiner's Answer was mailed June 28, 2005. In reply to the Examiner's Answer, Appellants submit this Reply Brief Under 37 C.F.R. § 41.41.

I. Breadth of the Claims

Appellants have noted that the scope of the claims on appeal is commensurate with the teachings of the specification and the knowledge possessed by persons of ordinary skill in the art. *See* Appeal Brief, pages 11 and 37. In addressing the breadth of the claims, the Examiner stated:

> Appellants argue that the scope of the invention is not broad[1] since the claims are limited to the treatment of an animal in need of treatment of neuroectodermal tumors, malignant astrocytomas, or glioblastomas and also specifies the characteristics of the antisense oligo-nucleotides and ribozymes. It is noted that even to such a *limited target* one in the art would be required to de novo/empirically screen thousands of potential antisense oligonucleotides and ribozymes where the specification does not exemplify or identify any specific cancer that is caused or been shown to be treatable as claimed.

Examiner's Answer, page 10, lines 6-13 (emphasis added). Thus, the Examiner has acknowledged that the claims recite a "limited target" to which the antisense oligonucleotides and ribozymes bind. It appears, therefore, that the Examiner agrees that the claims are not unduly broad.

Nonetheless, even for such a limited target, the Examiner has asserted that "one in the art would be required to de novo/empirically screen thousands of potential antisense oligonucleotides and ribozymes . . ." *See* Examiner's Answer, page 10, lines 10-12. Appellants do not agree that a person of ordinary skill in the art would have had to screen thousands of candidate oligonucleotides and ribozymes to identify those that would be effective in the practice of the claimed methods. The specification provides

[1] Appellants have never asserted that the claims are "not broad." As noted in the Appeal Brief at pages 11 and 37, the claims on appeal are not *unduly* broad.

exemplary regions of SEQ ID NO:1 to which the antisense oligonucleotides and ribozymes of the invention may be complementary. *See* specification, page 25, lines 18-24, and page 28, lines 20-24. The specification also sets forth three exemplary antisense oligonucleotide sequences (SEQ ID NOs: 9, 10 and 11). *See* specification, page 25, lines 24-28. Computer modeling programs for selecting antisense target sequences were also widely available in the art. *See* Appeal Brief, pages 17-18. With regard to ribozymes in particular, the specification describes specific structural elements that had been included in ribozymes that were shown to be effective *in vitro* for the specific cleavage of RNA sequences. *See* specification, page 29, lines 3-14.

In view of the specified portion of SEQ ID NO:1 recited in the claims, the teachings in the specification, and the tools and knowledge available in the art, it is unlikely that a skilled person would have had to screen thousands of oligonucleotides to identify antisense oligonucleotides and ribozymes for use in the practice of the claimed methods.

Additionally, the proper inquiry in an enablement analysis is whether making and/or using the claimed subject matter would have required *undue experimentation*. "[E]mpirically screen[ing] thousands of potential antisense oligonucleotides" does not, by itself, equate with undue experimentation. *See* M.P.E.P. § 2164.01 ("The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." Citing *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976)). Merely asserting that one would have had to "screen

thousands of potential antisense oligonucleotides" is not sufficient to support an enablement rejection.

The Examiner stated that "the specification does not exemplify or identify any specific cancer that is caused or been shown to be treatable as claimed. The specification shows [sic] does not identify any particular cancer where the inhibition of an NTP activity or expression is ameliorative." *See* Examiner's Answer, page 10, lines 12-15. As noted in the specification, however:

> AD7c-NTP is produced by neuroectodermal tumor cells, malignant astrocytoma cells, glioblastoma cells, and in relatively high concentrations (i.e., relative to controls) in brain tissue of AD patients. Thus AD7c-NTP antisense oligonucleotides of the present invention may be active in treatment against AD, as well as neuroectodermal tumors, malignant astrocytomas, and glioblastomas.

See specification, page 25, lines 2-7. In view of the AD7c-NTP expression pattern observed in neuroectodermal tumor cells, malignant astrocytoma cells and glioblastoma cells, it is logical to conclude that interfering with AD7c-NTP expression through the use of antisense oligonucleotides and ribozymes would effectively treat neuroectodermal tumors, malignant astrocytomas, and glioblastomas. No specific evidence has been presented to contradict this reasoning.

II. State of the Prior Art / Predictability

Appellants have presented ample evidence to indicate that the state of the art relating to the therapeutic use of antisense molecules, at the time of the effective filing date of the present application, was well established and sufficiently predictable. Appellants have pointed to at least eleven specific examples from the art demonstrating the successful therapeutic use of antisense oligonucleotides for a variety of conditions. *See* Appeal Brief, pages 13-16. The Examiner has not disputed the fact that there are successful applications of antisense molecules noted in the art. *See* Examiner's Answer, page 11, line 1.

The Examiner has nonetheless stated that "it is not agreed that these successes are demonstrative of a well-established and predictable art." *See* Examiner's Answer, page 11, lines 1-2. The Examiner has not provided a reasonable explanation, however, as to why the ability of others in the art to successfully construct and administer antisense-based therapeutic molecules does not indicate that the state of the art was well established and predictable. As noted in the Appeal Brief, the Examiner has failed to explain why it is believed that antisense therapies of the presently claimed invention would have required undue experimentation when, clearly, others were able to use antisense therapies in other contexts without undue experimentation. *See* Appeal Brief, pages 33-35.

Among the various examples cited by Appellants which demonstrate the successful use of antisense oligonucleotides are several examples that are discussed in the Agrawal reference. *See* Appeal Brief, pages 13-15. According to the Examiner, "the

Agrawal examples are directed to models and do not show the success in the treatment of any disease *per se*." *See* Examiner's Answer, page 11, lines 4-5. The Examples from Agrawal relate to antisense oligonucleotides that are administered to animals such as mice and rats expressing various disease-related phenotypes. *See* Appeal Brief, pages 13-15. The oligonucleotides were shown in these examples to cause both physiological effects (such as inhibiting tumor growth and lowering blood pressure) and behavioral effects (such as reducing anxiety-related behavior) in the animals. There is no reason to believe that the positive biological effects observed in the examples of Agrawal are not indicative of the results that would be observed when antisense oligonucleotides are administered in accordance with the practice of the claimed methods. Accordingly, the examples from the Agrawal reference reflect the advanced state of the art of antisense-based therapeutics.

Appellants have also pointed to several examples discussed in the Galderisi reference that involve the successful clinical use of antisense oligonucleotides to treat conditions and diseases in humans. *See* Appeal Brief, pages 13-14 (describing the successful use of antisense oligonucleotides for the treatment of ovarian, breast, prostate and colon cancer, as well as the treatment of chronic myelogenous leukemia). These clinical successes also reflect the overall advanced state of the art.

In addressing the examples from Agrawal and Galderisi, the Examiner stated that "[b]oth of the references discuss the successes in the art and both still indicate that much needs to be developed to make the application of antisense therapy predictable." *See* Examiner's Answer, page 11, lines 5-7. As explained in the Appeal Brief at page 20, and

discussed below, the statements from Agrawal that are relied upon by the Examiner relate specifically to the uptake of oligonucleotides in *cell culture systems*. The cited statements do not relate to the cellular uptake of oligonucleotides when administered to animals. Since the claimed methods specify the administration of antisense oligonucleotides or ribozymes to animals, the portions of Agrawal quoted by the Examiner cannot be relied upon to show that the field of the invention is unpredictable.

In addressing Appellants' arguments regarding Agrawal, the Examiner stated:

> Appellant argues that the Agrawal reference deals with the unpredictability of antisense in cells in culture, but it is noted that the instant specification fails to provide even cellular data, for example.

See Examiner's Answer, page 12, lines 20-22. The presence or absence of "cellular data" in the specification does not alter the fact that the cited portions of Agrawal relate to subject matter that is outside the scope of the present claims and therefore does not support an enablement rejection.

With regard to Galderisi, the portions of this reference quoted by the Examiner, at best, relate to the prior work that had gone into the development of antisense oligonucleotides as therapeutic agents and the desire to further optimize antisense technology. The Examiner appears to have taken certain statements of Galderisi out of context and has failed to acknowledge various statements that, overall, indicate the advanced state of the art. For example, the Examiner has cited Galderisi for the proposition that "[t]he use of antisense to modify gene expression is variable in both its

efficacy and reliability," and that "[m]ost of these concerns can be overcome by the development of a new generation of antisense molecules . . ." *See* Examiner's Answer, page 14, line 19, through page 15, line 2 (citing page 255, middle right column of Galderisi). In the paragraph immediately following the one cited by the Examiner, however, Galderisi explicitly emphasizes the advanced state of the art:

> Antisense ODNs already have shown their effectiveness in several preclinical studies. Phosphorothioate ODNs have reached phase I and II in clinical trials for the treatment of cancer and viral infections and have demonstrated an acceptable safety and pharmacokinetic profile for continuing their development. The new drug Vitravene, which is based on an antisense mechanism and is commercially available in the United States, has shown that some substantial successes can be reached with the antisense technique.

Galderisi, page 255, middle right column. As a whole, Galderisi indicates that the state of the art of antisense-based therapeutics was advanced at the time of the effective filing date of the present application.

It is undisputed that both Agrawal and Galderisi describe multiple examples of the successful use of antisense oligonucleotides for therapeutic purposes. Persons in the art were therefore able to effectively make and use a variety of antisense-based molecules for a variety of purposes notwithstanding any technical considerations that

may have been acknowledged in the art. Thus, neither Agrawal nor Galderisi, when considered in their entireties, indicate that the art of antisense-based therapeutics was unpredictable.

Appellants have pointed to the discussion in Galderisi regarding the antisense-based drug, Vitravene. *See* Appeal Brief, pages 15-16. As noted by Galderisi, Vitravene is an antisense oligonucleotide approved for marketing in the United States and indicated for the local treatment of cytomegalovirus retinitis in patients with AIDS. *See id.* Vitravene is another example which demonstrates that the field of antisense-based therapeutics was well established at the time of the effective filing date of the present application. With respect to this example, the Examiner stated that "[t]he antisense oligonucleotide of Vitravene™ is administered intravitrally and does not suffer from the problems associated with delivery as asserted in the rejection of record." *See* Examiner's Answer, page 11, lines 9-11. The Examiner, however, has not presented any specific evidence to support this assertion. For example, the Examiner has not identified the specific "problems" allegedly associated with antisense delivery in general that are not associated with the administration of Vitravene in particular. Nor has the Examiner presented evidence to indicate why such alleged "problems" would be encountered when practicing the currently claimed methods but not when administering Vitravene. Moreover, no evidence has been presented to show that such alleged "problems" are of a magnitude that would amount to undue experimentation.

The Examiner has also cited portions of the Branch reference to indicate the level of alleged unpredictability in the art. The Examiner has relied on Branch for issues

relating to "non-antisense effects." As pointed out in the Appeal Brief, Branch indicates that non-antisense effects may actually be beneficial in clinical settings. *See* Appeal Brief, pages 21-22. Thus, Branch does not support the contention that the field of the present invention is unpredictable. In addressing Appellants' analysis of the Branch reference, the Examiner stated:

> Applicant asserts that the Branch reference teaches that non-antisense effects might be advantageous, however, there has been no disclosure of or discussion of non-antisense in the instantly claimed invention being an advantage that overcomes the unpredictability of the art, for example.

See Examiner's Answer, page 12, line 22, through page 13, line 4. The pertinent issue is not whether Appellants' specification discusses non-antisense effects of oligonucleotides, but whether Branch supports the enablement rejection by showing that the field of the invention is unpredictable. The Examiner, in an attempt to establish unpredictability in the art, has cited sentences from Branch relating to non-antisense effects. Since Branch does not indicate that non-antisense effects render the administration of antisense molecules unpredictable in clinical settings, and since Branch states that non-antisense effects may actually be beneficial in such contexts, Branch does not support the rejection.

As noted in the Appeal Brief, the basic aspects of antisense-based therapeutics (*i.e.*, designing an appropriate antisense molecule or ribozyme and delivering such

molecules to cells) are not unpredictable. *See* Appeal Brief, pages 16-19 and 39-40. With respect to cellular delivery of antisense molecules, the Examiner stated that:

> Appellant also argues that cellular delivery of antisense oligonucleotides was predictable at the time of filing. *Delivery to cells in culture was indeed more predictable than delivery to an animal as is made clear from the references and the rejection of record.* The claimed invention is drawn to delivery to an animal not cells in culture.

See Examiner's Answer, page 12, lines 15-18 (emphasis added). Appellants are not aware of any evidence on the record (and the Examiner has not pointed to any) that indicates that the delivery of antisense molecules to cells in culture was "more predictable than delivery to an animal." In fact, the evidence appears to suggest the opposite: According to Agrawal, "[i]t is clear from some of the studies mentioned in this review and many other published reports that PS-oligonucleotides show more sequence-specific antisense activity in *animal models* than in cell culture experiments." *See* Appeal Brief, page 20 (citing Agrawal at page 384, middle right column). Thus, if anything, the evidence of record suggest that antisense-based therapeutics behave more predictably when administered to animals than when administered to cells in culture.

In summary, neither the Examiner's Answer nor any evidence of record contradicts Appellants' position that the field of the invention was well established and predictable at the time of the effective filing date of the present application.

III. Quantity of Experimentation Needed

With respect to the amount of experimentation needed to practice the claimed methods, the Examiner stated that:

> In this case, the more or less standard (albeit empirical and unpredictable) nature of screening for an active antisense in cells and the non-routine experimentation required to find a means of providing a sufficient amount of an antisense that will be effective in an animal and targeted to a specific tissue and/or cell for sufficient time to treat a condition required to expand the scope of an enabled invention is outweighed by the sheer quantity of experimentation to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which the experimentation should proceed.

See Examiner's Answer, page 12, lines 5-13. The above-quoted statements are unsupported by the evidence of record and do not provide any basis for a legally valid enablement rejection.

First, the evidence of record does not indicate that "screening for an active antisense in cells" was unpredictable. As noted in the Appeal Brief, screening methods

were recognized in the art as being effective for identifying target-specific antisense oligonucleotides. *See* Appeal Brief, pages 31-32.

Second, the evidence of record does not support the assertion that "non-routine experimentation" would have been "required to find a means of providing a sufficient amount of an antisense that will be effective in an animal and targeted to a specific tissue and/or cell for sufficient time to treat a condition . . ." As noted repeatedly by Appellants, at the time of the effective filing date of the present application there were multiple examples in the art of the successful use of antisense oligonucleotides for therapeutic purposes. There is nothing to suggest that "non-routine experimentation" was required to practice the methods shown in these examples. There is certainly no evidence in any of the cited examples to suggest that "find[ing] a means of providing a sufficient amount of an antisense" would have required "non-routine experimentation." The commonplace application of antisense methods in the art strongly suggests that determining parameters such as cellular delivery, amount of oligonucleotide and timing of administration, involved nothing more than the use of routine techniques.

The Examiner has referred to the "sheer quantity of experimentation to practice the full scope of the claims." *See* Examiner's Answer, page 12, lines 10-11. This is another instance of a conclusion that is not supported by the evidence and is actually contradicted by the evidence cited by Appellants.

The evidence of record indicates that only a modest amount of experimentation would have been needed to select an effective target sequence within SEQ ID NO:1 to which the antisense oligonucleotides and ribozymes of the invention are complementary.

See, e.g., Appeal Brief, pages 30-32 (discussing elements of the claims and teachings in the specification that would have significantly limited the amount of experimentation needed to identify an acceptable target sequence, and the existence of screening and computer modeling approaches that were routinely practiced in the art for identifying effective antisense oligonucleotides), and page 39 (discussing the structural domains of ribozymes disclosed in the specification that would have guided one of ordinary skill in the art in making ribozymes for use in the methods of the invention). The evidence also indicates that delivering antisense molecules and ribozymes to cells (*e.g.*, neuronal cells) in animals would not have required a large quantity of experimentation. *See, e.g.*, Appeal Brief, page 33 (discussing examples from the art in which antisense molecules were successfully administered for the treatment of neuronal defects), and page 40 (discussing well known strategies for increasing the efficiency of cellular delivery of ribozymes). Thus, it is clear that the two basic aspects of antisense-based therapeutics (designing appropriate antisense-based molecules and delivering such molecules to cells) did not require a large quantity of experimentation. Any experimentation that was involved in these aspects cannot be regarded as "non-routine."

IV. Amount of Guidance Provided in the Specification

With respect to the amount of guidance provided in the specification, the Examiner asserted that "the specification provides general options of where one might start without any specific guidance on how to treat a specific disease with a predictable delivery means with an antisense oligonucleotide that would predictably function in its

targeted environment." *See* Examiner's Answer, page 11, lines 16-19. The Examiner also stated:

> Appellant cites the specification at pages 26, 30, 31 and 32 to show that the specification provides guidance for delivery. It is noted that the text is general and requires one in the art to make de novo determinations for a suitable delivery means for any particular disease where there is no specific guidance for the treatment of any particular disease, for example.

See Examiner's Answer, page 13, lines 5-9. The teachings in the specification, however, provide more than ample guidance for practicing the claimed methods, especially in view of the vast quantity of knowledge that was available in the art for making and using antisense oligonucleotides and ribozymes.

The Examiner, in assessing the teachings of the specification, appears to have ignored the well established principle of patent law that "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." *See* M.P.E.P. § 2164.05(a) (citing, *inter alia*, *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991)). The minute details of making, formulating and administering antisense oligonucleotides and ribozymes, in general, were well known to persons of ordinary skill in the art, as evidenced by the numerous examples of the successful use of antisense-based therapeutics. There is no evidence to suggest that such general

knowledge in the art could not have been effectively applied in the context of the present invention. Thus, when considered in light of the knowledge possessed by persons of ordinary skill in the art, the specification clearly provides more than adequate guidance for practicing the claimed methods.

V. Summary/Conclusion

The Examiner's Answer fails to address a critical fact that is emphasized throughout the record and that strongly argues in favor of the enablement of the present invention; namely, that others were able to routinely make and use antisense-based therapeutic molecules in other contexts. The Examiner has not pointed to any *unique aspect* of the currently claimed methods that would have caused one of ordinary skill in the art to encounter difficulties that were not encountered in other contexts and that would have required undue experimentation to surmount.

In light of the arguments above, as well as those set forth in Appellants' Brief on Appeal filed April 8, 2005, Appellants respectfully submit that the final rejection of claims 35, 37-43 and 45 under 35 U.S.C. § 112, first paragraph, is improper and should be reversed.

Respectfully submitted,

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Date: AUG. 19, 2005

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